

Diagnostic Testing for Migraine and Other Primary Headaches

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KEYWORDS

- Headache • Diagnostic testing • Magnetic resonance imaging
- Computerized tomography • Migraine
- Trigeminal autonomic cephalalgias • Hemicrania continua
- New daily persistent headache

Most primary headaches can be diagnosed without diagnostic testing using a comprehensive history and neurologic and focused general physical examinations.

In some cases, however, diagnostic testing is necessary to distinguish primary from secondary causes that may share similar features. The differential diagnosis is one of the longest in all of medicine, with more than 300 different types and causes. In this article, the reasons for diagnostic testing and the use of neuroimaging, electroencephalography, lumbar puncture, and blood testing are evaluated. The use of diagnostic testing in adults and children who have a normal neurologic examination, migraine, trigeminal autonomic cephalalgias (TACs), hemicrania continua (HC), and new daily persistent headache (NDPH) are reviewed.

REASONS FOR DIAGNOSTIC TESTING

The indications for diagnostic testing are variable and neurologists must make decisions on a case-by-case basis when presented with a suspected primary headache if secondary headache is a consideration. Clinical situations where neurologists consider diagnostic testing are listed in **Box 1**.

There are many other reasons why neurologists recommend diagnostic testing: “our stubborn quest for diagnostic certainty;”¹ faulty cognitive reasoning; the medical decision rule that it is better to impute disease than to risk overlooking it busy practice conditions where tests are ordered as a shortcut; patient expectations; financial incentives; professional peer pressure, where recommendations for routine and esoteric tests are expected as a demonstration of competence; and medicolegal issues.^{2,3} The attitudes and demands of patients and families and the practice of defensive medicine are especially important reasons in the case of headaches. In the era of managed care, equally compelling reasons for not ordering diagnostic studies include

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Box 1**Reasons to consider neuroimaging for headaches***Temporal and headache features*

1. The “first or worst” headache
2. Subacute headaches with increasing frequency or severity
3. A progressive headache or NDPH
4. Chronic daily headache
5. Headaches always on the same side
6. Headaches not responding to treatment

Demographics

7. New-onset headaches in patients who have cancer or who test positive for HIV infection
8. New-onset headaches after age 50
9. Patients who have headaches and seizures

Associated symptoms and signs

10. Headaches associated with symptoms and signs, such as fever, stiff neck, nausea, and vomiting
11. Headaches other than migraine with aura associated with focal neurologic symptoms or signs
12. Headaches associated with papilledema, cognitive impairment, or personality change

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physician fears of deselection and at-risk capitation. Lack of funds and underinsurance continue to be barriers to appropriate diagnostic testing for many patients.

DIAGNOSTIC TESTING OPTIONS***CT versus MRI***

CT detects most abnormalities that may cause headaches. CT generally is preferred to MRI for evaluation of acute subarachnoid hemorrhage, acute head trauma, and bony abnormalities. There are several disorders, however, that may be missed on routine CT of the head, including vascular disease, neoplastic disease, cervicomedullary lesions, and infections (**Box 2**). MRI is more sensitive than CT in the detection of posterior fossa and cervicomedullary lesions, ischemia, white matter abnormalities (WMA), cerebral venous thrombosis (CVT), subdural and epidural hematomas, neoplasms (especially in the posterior fossa), meningeal disease (such as carcinomatosis, diffuse meningeal enhancement in low cerebrospinal fluid [CSF] pressure syndrome, and sarcoid), and cerebritis and brain abscess. Pituitary pathology is more likely to be detected on a routine MRI of the brain than a routine CT.

Another concern with CT is exposure to ionizing radiation. The average radiation dose of a CT scan of the head (with or without contrast—both studies double the dose) is an effective dose of 2.0 millisieverts (mSv), which is equivalent to 100 chest radiographs.⁴ The most common malignancies associated with radiation exposure include leukemia and breast, thyroid, lung, and stomach cancers. The latency period for solid tumors usually is long, an average of 10 to 20 years, with a persistent lifelong risk. Leukemia has an earlier latency period with an increased risk 2 to 5 years after

Box 2**Causes of headache that can be missed on routine CT scan of the head***Vascular disease*

Saccular aneurysms

AVMs (especially posterior fossa)

Subarachnoid hemorrhage

Carotid or vertebral artery dissections

Infarcts

CVT

Vasculitis

WMA

Subdural and epidural hematomas

Neoplastic disease

Neoplasms (especially in the posterior fossa)

Meningeal carcinomatosis

Pituitary tumor and hemorrhage

Cervicomedullary lesions

Chiari malformations

Foramen magnum meningioma

Infections

Paranasal sinusitis

Meningoencephalitis

Cerebritis and brain abscess

Other

Low CSF pressure syndrome

Idiopathic hypertrophic pachymeningitis

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radiation exposure. The pediatric population is at increased risk, as a result of increased radiosensitivity and more years of remaining life, for potentially developing cancer. Consider the radiation exposure of some patients who have multiple trips to an emergency department, have migraine and multiple CT scans, and also have multiple CT scans of the head and sinuses in an outpatient setting. For a single CT scan of the head, the estimated lifetime attributable risk for death from cancer by age is approximately as follows: age 10 years, 0.025%; age 20 years, 0.01%; and age 50 years, 0.003%.⁵ Although these are small numbers, are individual studies justified? Up to 2% of all cancer deaths in the United States may be attributable to radiation exposure associated with CT use. The Food and Drug Administration has estimated that exposure to 10 mSv (equivalent to one CT of the abdomen) may be associated with an increased risk for developing fatal cancer in one of every 2000 patients [FDA].⁶

Thus, MRI generally is preferred over CT for evaluation of headaches. The yield of MRI may vary depending on the field strength of the magnet, the use of paramagnetic

contrast, the selection of acquisition sequences, and the use of magnetic resonance (MR) angiography and MR venography (MRV). MRI may be contraindicated, however, in the presence of an aneurysm clip or pacemaker. In addition, approximately 8% of patients are claustrophobic, approximately 2% to the point at which they cannot tolerate the study.

Neuroimaging During Pregnancy and Lactation

When there are appropriate indications, neuroimaging should be performed during pregnancy.⁷ With the use of lead shielding, a standard CT scan of the head exposes the uterus to less than 1 mrad. The radiation dose for a typical cervical or intracranial arteriogram is less than 1 mrad. The fetus is most susceptible to the teratogenic effects of radiation between the second and 20th weeks of embryonic age⁸ with a threshold radiation dose estimated at between 5 and 15 rad.⁹ Although there is no known risk associated with iodinated contrast use during pregnancy, contrast should be avoided without indication.¹⁰

MRI is more sensitive for rare disorders that may occur during pregnancy, such as pituitary apoplexy, CVT (with the addition of MRV), and metastatic choriocarcinoma. There is no known risk associated with MRI during pregnancy¹¹ but there is some controversy because the magnets induce an electric field and raise the core temperature slightly (less than 1°C). A survey of pregnant MRI workers found no adverse fetal outcome,¹² and no adverse fetal effects from MRI have been documented to date. Children exposed in utero at 1.5 tesla were found to have no exposure-related abnormalities at 9 months of age¹³ and up to 9 years of age.¹⁴

According to the 2007 American College of Radiology Guidance Document for Safe Practices,¹⁰

Present data have not conclusively documented any deleterious effects of MR imaging exposure on the developing fetus. Therefore, no special consideration is recommended for the first, versus any other, trimester in pregnancy. Pregnant patients can be accepted to undergo MR scans at any stage of pregnancy if, in the determination of a level 2 MR personnel-designated attending radiologist, the risk-benefit ratio to the patient warrants that the study be performed. The radiologist should confer with the referring physician and document the following in the radiology report or the patient's medical record:

1. *The information requested from the MR study cannot be acquired via nonionizing means (eg, ultrasonography).*
2. *The data are needed to potentially affect the care of the patient or fetus during the pregnancy.*
3. *The referring physician does not feel it is prudent to wait until the patient is no longer pregnant to obtain these data.*

*...MR contrast agents should not be routinely provided to pregnant patients. The decision to administer a gadolinium-based MR contrast agent to pregnant patients should be accompanied by a well-documented and thoughtful risk-benefit analysis.*¹⁵

There is no known risk of gadolinium to the fetus.¹⁰

Lactating women may be advised to discard breast milk for 24 hours after receiving intravenous iodinated contrast or gadolinium. Only a tiny fraction of iodinated contrast or gadolinium entering the infant gut is actually absorbed, however. "The very small potential risk associated with absorption of contrast medium may be insufficient to warrant stopping breast-feeding for 24 hours after either iodinated or gadolinium contrast agents."¹¹

Electroencephalography

The electroencephalogram (EEG) was a standard test for evaluation of headaches in the pre-CT scan era. Gronseth and Greenberg¹⁶ reviewed the literature from 1941 to 1994 on the usefulness of EEG in the evaluation of patients who had headache. Most of the articles had serious methodologic flaws. The only significant abnormality reported in studies with a relatively nonflawed design was prominent driving in response to photic stimulation (the H-response) in migraineurs who had a sensitivity ranging from 26%¹⁷ to 100%¹⁸ and a specificity from 80%¹⁹ to 91%.¹⁸ This finding, although interesting, is not necessary for the clinical diagnosis of migraine. If the purpose of the EEG is to exclude an underlying structural lesion, such as a neoplasm, CT or MRI imaging is far superior.

A report of the Quality Standards Subcommittee of the American Academy of Neurology (AAN) suggests the following practice parameter: "The electroencephalogram (EEG) is not useful in the routine evaluation of patients with headache. This does not exclude the use of EEG to evaluate headache patients with associated symptoms suggesting a seizure disorder such as atypical migrainous aura or episodic loss of consciousness. Assuming head imaging capabilities are readily available, EEG is not recommended to exclude a structural cause for headache."²⁰

A report of the Quality Standards Subcommittee of the AAN and the Practice Committee of the Child Neurology Society²¹ makes the following pediatric recommendations: "EEG is not recommended in the routine evaluation of a child with recurrent headaches, as it is unlikely to provide an etiology, improve diagnostic yield, or distinguish migraine from other types of headaches (Level C; class II and class III evidence)."

Lumbar Puncture

MRI or CT scan always is performed before a lumbar puncture for evaluation of headaches except in some cases where acute meningitis is suspected. Lumbar puncture can be diagnostic for meningitis or encephalitis, meningeal carcinomatosis or lymphomatosis, subarachnoid hemorrhage, and high (eg, pseudotumor cerebri) or low CSF pressure. In cases of blood dyscrasias, the platelet count should be 50,000 or greater before safely performing a lumbar puncture. The CSF opening pressure always should be measured when investigating headaches. When measuring the opening pressure, it is important for patients to relax and at least partially extend the head and legs to avoid recording a falsely elevated pressure.

After neuroimaging is performed, lumbar puncture often is indicated in the following circumstances: the first or worst headache, headache with fever or other symptoms or signs suggesting an infectious cause, a subacute or progressive headache (eg, in an HIV-positive patient or a person who has carcinoma), and an atypical chronic headache (eg, to rule out pseudotumor cerebri in an obese woman who does not have papilledema).

There are many potential complications of lumbar puncture, the most common of which is low CSF pressure headache, which occurs approximately 30% of the time using the conventional bevel-tip or Quincke needle.²² The risk for headache can be reduced dramatically to approximately 5% to 10% by using an atraumatic needle, such as the Sprotte or Whitacre, and replacing the stylet before withdrawing the needle.²³

Blood Tests

Blood tests generally are not helpful for diagnosis of headaches. There are many indications, however, such as the following: erythrocyte sedimentation rate or C-reactive

protein to consider the possibility of temporal arteritis in a person 50 years or older who has new-onset migraine, as only 2% of migraineurs have an onset at age 50 years or older; erythrocyte sedimentation rate, rheumatoid arthritis factor, and antinuclear antibody test in patients who have headache and arthralgia to evaluate for possible collagen vascular disease, such as lupus;²⁴ monospot in teenagers who have headaches, sore throat, and cervical adenopathy; complete blood cell count (CBC), liver function tests, HIV test, or Lyme antibody test in some patients who have a suspected infectious basis; an anticardiolipin antibody and lupus anticoagulant in migraineurs who have extensive WMA on MRI; thyroid-stimulating hormone because headache may be a symptom in 14% of cases of hypothyroidism; CBC because headache may be a symptom when the hemoglobin concentration is reduced by one half or more; serum urea nitrogen and creatinine to exclude renal failure, which can cause headache; serum calcium because hypercalcemia can be associated with headaches; CBC and platelets because thrombotic thrombocytopenic purpura can cause headaches; and endocrine studies in patients who have headaches and a pituitary tumor.

Additionally, blood tests may be indicated as a baseline and for monitoring for certain medications, such as valproic acid for migraine prophylaxis, carbamazepine for trigeminal neuralgia, and lithium for chronic cluster headaches.

HEADACHES AND A NORMAL NEUROLOGIC EXAMINATION

Neuroimaging Studies in Adults

The yield of abnormal neuroimaging studies in studies of patients who have headaches as the only neurologic symptom and normal neurologic examinations depends on several factors, including the duration of the headache, study design (prospective versus retrospective), who orders the scan, and the type of scan performed.²⁵ The percentage of abnormal scans is higher when ordered by neurologists²⁶ or a tertiary care center²⁷ compared with primary care physicians and represents case selection bias. In reported CT scan series, the yield may vary depending on the generation of scanner and whether or not iodinated contrast was used. The yield of MRI may vary depending on the field strength of the magnet, the use of paramagnetic contrast, the selection of acquisition sequences, and the use of MR angiography.

Frishberg²⁵ reviewed eight CT scan studies of 1825 patients who had unspecified headache types and varying durations of headache.²⁶⁻³³ The summarized findings from these studies is combined with four additional studies of 1566 CT scans in patients who had headache and normal neurologic examinations³⁴⁻³⁷ for a total of 3389 scans. The overall percentages of various pathologies is as follows: brain tumors, 1%; arteriovenous malformations (AVMs), 0.2%; hydrocephalus, 0.3%; aneurysm, 0.1%; subdural hematoma, 0.2%; and strokes (including chronic ischemic process), 1.1%.

There are four studies of patients who had chronic headaches and a normal neurologic examination. Combining three of these studies with 1282 patients, the only clinically significant pathology was one low-grade glioma and one saccular aneurysm.^{33,34,36} A fourth study of 363 consecutive CT scans, however, found significant pathology in 11 (3%), including two of intraventricular cysts, four meningiomas, and five malignant neoplasms.³⁵

Weingarten and colleagues³³ extrapolated various types of data from 100,800 adult patients who belonged to a health maintenance organization. The estimated prevalence (in patients who had chronic headache and a normal neurologic examination) of a CT scan demonstrating an abnormality requiring neurosurgical intervention may have been as low as 0.01%. It is not certain whether or not detection of additional

pathology on MRI scan would change this percentage. For example, complaints of headache with a normal neurologic examination may be seen in patients who have Chiari type I malformation, which is easily detected on MRI but not CT scans.³⁸ Pituitary hemorrhage can produce a migraine-like acute headache with a normal neurologic examination.³⁹ Pituitary infarction, with severe headache, photophobia, and CSF pleocytosis, initially can be similar to aseptic meningitis or meningococcal meningitis.⁴⁰ Pituitary pathology is more likely to be detected on a routine MRI than CT scan.

Wang and coworkers⁴¹ retrospectively reviewed the medical records and MRI images of 402 adult patients (286 women and 116 men) who had been evaluated by the neurology service and who had a primary complaint of chronic headache (a duration of 3 months or more) and no other neurologic symptoms or findings. Major abnormalities (a mass, caused mass effect, or was believed the likely cause of patient's headache) were found in 15 patients (3.7%) and included glioma, meningioma, metastases, subdural hematoma, AVM, hydrocephalus (three patients), and Chiari I malformations (two patients). They were found in 0.6% of patients who had migraine, 1.4% of those who had tension headaches, 14.1% of those who had atypical headaches, and 3.8% of those who had other types of headaches.

Tsushima and Endo⁴² retrospectively reviewed the clinical data and MR studies of 306 adult patients (136 men and 170 woman) all of whom were referred for MRI evaluation of chronic or recurrent headache with a duration of 1 month or more, had no other neurologic symptoms or focal findings at physical examination, and had no prior head surgery, head trauma, or seizure: 55.2% had no abnormalities, 44.1% had minor abnormalities, and 0.7% (two) had clinically significant abnormalities (pituitary macroadenoma and subdural hematoma). Neither contrast material enhancement ($n = 195$) nor repeated MRI ($n = 23$) contributed to the diagnosis.

Sempere and colleagues⁴³ reported a study of 1876 consecutive patients (1243 women and 633 men), ages 15 or older, mean age 38 years, who had headaches that had an onset at least 4 weeks previously and who were referred to two neurology clinics in Spain. One third of the headaches were new onset, and two thirds had been present for more than 1 year. Subjects had the following types: migraine (49%), tension (35.4%), cluster (1.1%), posttraumatic (3.7%), and indeterminate (10.8%). Normal neurologic examinations were found in 99.2% of the patients. CT scan was performed in 1432 patients and MRI in 580; 136 patients underwent both studies.

Neuroimaging studies detected significant lesions in 22 patients (1.2%), of whom 17 had a normal neurologic examination. The only variable or red flag associated with a higher probability of intracranial abnormalities was an abnormal neurologic examination with a likelihood ratio of 42. The diagnoses in these 17 patients were pituitary adenoma ($n = 3$), large arachnoid cyst ($n = 2$), meningioma ($n = 2$), hydrocephalus ($n = 2$), and Arnold-Chiari type I malformation, ischemic stroke, cavernous angioma, AVM, low-grade astrocytoma, brainstem glioma, colloid cyst, and posterior fossa papilloma (one of each). Of these 17 patients, eight were treated surgically for hydrocephalus ($n = 2$), and pituitary adenoma, large arachnoid cyst, meningioma, AVM, colloid cyst, and papilloma (one of each).

The rate of significant intracranial abnormalities in patients who had headache and normal neurologic examination was 0.9%. Neuroimaging studies discovered incidental findings in 14 patients (75%): three pineal cysts, three intracranial lipomas, and eight arachnoid cysts. The yield of neuroimaging studies was higher in the group with indeterminate headache (3.7%) than in the migraine (0.4%) or tension-type headache (0.8%) groups. The study does not provide information on WMA in migraineurs. MRI performed in patients who had normal CT revealed significant lesions in two

cases: a small meningioma and an acoustic neurinoma. No saccular aneurysms were detected; MR angiography was not obtained.

The studies do not give information about the detection of paranasal sinus disease, however, which may be the cause of some headaches. For example, sphenoid sinusitis may cause a severe, intractable, new-onset headache that interferes with sleep and is not relieved by simple analgesics. The headache may increase in severity with no specific location. There may be associated pain or paraesthesias in the facial distribution of the fifth nerve and photophobia or eye tearing with or without fever or nasal drainage. The headache may mimic other causes, such as migraine or meningitis.⁴⁴

Neuroimaging in Children

Several studies have investigated the findings of neuroimaging in children who had headaches. Dooley and colleagues reported the retrospective findings of CT scans of 41 children who had headaches and normal neurologic examinations referred to a secondary or tertiary care facility.⁴⁵ Only one scan was abnormal demonstrating a choroid plexus papilloma. Chu and Shinnar⁴⁶ obtained brain imaging studies in 30 children, ages 7 or younger, who had headaches and were referred to pediatric neurologists. The studies were normal except for five that had incidental findings.

Maytal and coworkers⁴⁷ obtained MRI or CT scans or both in 78 children, ages 3 to 18, who had headaches. With the exception of six patients, the neurologic examinations were normal. The studies were normal except for incidental cerebral abnormalities in four and mucoperiosteal thickening of the paranasal sinuses in seven. Wöber-Bingöl and colleagues⁴⁸ prospectively obtained MRI scans in 96 children, ages 5 to 18, who had headaches and normal neurologic examinations and who were referred to an outpatient headache clinic. The studies were normal except for 17 (17.7%) that had incidental findings.

Medina and colleagues⁴⁹ retrospectively reported MRI findings in 315 children, ages 3 to 20 (mean 11 years), who had headaches. The neurologic examinations were abnormal in 89 patients. Thirteen (4%) had surgical space-occupying lesions. After analyzing risk factors for these lesions and the prior literature, Medina and colleagues suggested guidelines for neuroimaging in children who have headache (**Box 3**).

Lewis and Dorbad⁵⁰ retrospectively reviewed records of children, ages 6 to 18, who had migraine and chronic daily headache with normal examinations. Of 54 patients who had migraine who underwent CT (42) or MRI (12) scans, the yield of abnormalities was 3.7%, none clinically relevant. Of 25 patients who had chronic daily headache who underwent CT (17) or MRI (8) scans, the yield of abnormalities was 16%, none clinically relevant.

Carlos and colleagues,⁵¹ in a retrospective chart review, identified all pediatric migraine patients who had a CT or MRI to investigate their headaches. Ages ranged from 3 to 18. Of the 93 patients, 35 had CT, 14 had MRI, and 9 had both. Twenty-two had abnormalities but none was believed related to the patients' headaches. Alehan⁵² prospectively obtained neuroimaging (49 MRI scans and 11 CT scans) in 60 of 72 consecutive children diagnosed with migraine or tension-type headaches. Ten percent had findings related to their headache with no neoplasms, and no patients required surgery.

Mazzotta and colleagues⁵³ performed a prospective study at several pediatric headache centers of 6535 first-time referrals; patients up to age 18 were studied. Based on the indications of the diagnostic flow-chart, 1485 underwent neuroimaging testing. Incidental findings were observed in 138 (9.3%) subjects. Abnormal results were observed in 273 (18.5%) subjects. Findings that led to diagnosis of secondary

Box 3**Reasons to consider neuroimaging for children who have headaches**

1. Persistent headaches of less than 6-months' duration that do not respond to medical treatment
2. Headache associated with abnormal neurologic findings, especially if accompanied by papilledema, nystagmus, or gait or motor abnormalities
3. Persistent headaches associated with an absent family history of migraine
4. Persistent headache associated with substantial episodes of confusion, disorientation, or emesis
5. Headaches that awaken a child repeatedly from sleep or occur immediately on awakening
6. Family history or medical history of disorders that may predispose one to central nervous system lesions and clinical or laboratory findings suggestive of central nervous system involvement

Data from Medina S, Pinter JD, Zurakowski D, et al. Children with headache: clinical predictors of surgical space-occupying lesions and the role of neuroimaging. Radiology 1997;202:819–24.

headache were observed in 135 (9.1%), including sinusitis in 57% and intracranial space-occupying lesions in 17.4%.

A report of the Quality Standards Subcommittee of the AAN and the Practice Committee of the Child Neurology Society²¹ makes the following recommendations:

1. Obtaining a neuroimaging study on a routine basis is not indicated in children who have recurrent headaches and a normal neurologic examination (level B; class II and class III evidence).
2. Neuroimaging should be considered in children who have an abnormal neurologic examination (eg, focal findings, signs of increased intracranial pressure, significant alteration of consciousness), the coexistence of seizures, or both (level B; class II and class III evidence).
3. Neuroimaging should be considered in children in whom there are historical features to suggest the recent onset of severe headache or change in the type of headache or if there are associated features that suggest neurologic dysfunction (level B; class II and class III evidence).

American Academy of Neurology Practice Parameter

A report of the Quality Standards Subcommittee of the AAN⁵⁴ makes the following recommendations for nonacute headache:

The following symptoms significantly increased the odds of finding a significant abnormality on neuroimaging in patients with nonacute headache: rapidly increasing headache frequency; history of lack of coordination; history of localized neurologic signs or a history such as subjective numbness or tingling; and history of headache causing awakening from sleep (although this can occur with migraine and cluster headache). The absence of these symptoms did not significantly lower the odds of finding a significant abnormality on neuroimaging.

Consider Neuroimaging in Patients with an unexplained abnormal finding on the neurologic examination (Grade B).

Consider neuroimaging in patients with atypical headache features or headaches that do not fulfill the strict definition of migraine or other primary headache

disorder (or have some additional risk factor, such as immune deficiency), when a lower threshold for neuroimaging may be applied (Grade C).

No evidence-based recommendations are established for the following: presence or absence of neurologic symptoms (Grade C); tension-type headache (Grade C); and relative sensitivity of MRI as compared with CT in the evaluation of migraine or other nonacute headache (Grade C).

Risk/Benefit and Cost/Benefit of Neuroimaging

Table 1 summarizes the estimated risks and benefits of neuroimaging in patients who have headaches and normal neurologic examinations. (Radiation exposure and the increased long-term risk for are cancer discussed previously.) Although for many patients the scan helps to relieve anxiety, for others the scan may produce anxiety when nonspecific abnormalities are found, such as incidental anatomic variants or white matter lesions. I suspect that many neurologists have seen patients who have isolated headaches referred by primary care physicians with a request to rule out multiple sclerosis when white matter lesions are detected.

Although the cost of finding significant pathology is high, the cost of neuroimaging is decreasing significantly under some managed care contracts. Cost/benefit estimates should include the cost to physicians of malpractice suits filed when patients who have significant pathology do not have neuroimaging and the cost to patients and society of premature death and disability of undetected treatable lesions.

Table 1			
Balance sheet. CT or MRI in patients with headaches and normal neurologic examinations.			
Technology: CT with intravenous contrast or MRI without contrast. Indications: (1) migraine and (2) any headache			
	CT	MRI	No Test
Health outcomes			
Benefits			
Discovery of potentially treatable lesions			
1. Migraine	0.3%	0.4%	0
2. Any headache	2.4%	2.4%	0
Relief of anxiety	30%	30%	0
Harms			
Iodine reaction			
Mild	10%		
Moderate	1%		
Severe	0.01%		
Death	0.002%		
Claustrophobia			
Mild	5%	15%	0
Moderate (needs sedation)	1%	5%–10%	
Severe (unable to comply)	1%–2%		
False-positive studies	No data	No data	
Cost (charges)	Varies widely depending on payor		

Data from Frishberg BM. The utility of neuroimaging in the evaluation of headache in patients with normal neurologic examinations. *Neurology* 1994;44:1196.

NEUROIMAGING IN MIGRAINE

Incidence of Pathology

Frishberg²⁵ reviewed four CT scan studies,^{55–58} four MRI scan studies,^{59–62} and one combined MRI and CT scan study⁶³ of 897 scans of patients who had migraine. These findings are combined with more recent reports of one CT scan study of 284 patients³⁶ and six studies of MRI scans of 444 patients^{64–69} for a total of 1625 scans of patients who had various types of migraine. Other than WMA, the studies showed no significant pathology except for four brain tumors (three of which were incidental findings) and one AVM (in a patient who had migraine and a seizure disorder). Sempere⁴³ found a similarly low yield of 0.4%.

White Matter Abnormalities and Subclinical Infarcts

Fourteen MRI studies have investigated WMA on scans of patients who had migraine. WMA are foci of hyperintensity on proton density and T2-weighted images in the deep and periventricular white matter resulting from interstitial edema or perivascular demyelination. WMA are easily detected on MRI but are not seen on CT scan.⁶³

The percentages of WMA for all types of migraine range from 12%⁶¹ to 46%.⁶² WMA have been reported as more frequent in the frontal region of the centrum semiovale^{59,65} and no more frequent⁶⁷ than in the white matter of the parietal, temporal, and occipital lobes. Six of the eight studies using controls found a higher incidence of WMA in migraineurs. The incidence of WMA in controls ranged from 0%⁷⁰ to 14%.⁶⁶ One small study reported a similar incidence of WMA in patients who had tension-type headaches, 34.3%, as in those who had migraine, 32.1%, and greater than the 7.4% in controls.⁶⁵

Four studies found similar percentages of WMA comparing migraine with aura to migraine without,^{64,65,67,71} whereas two reported a higher percentage in migraine with aura.^{59,66} Three small studies of basilar migraine found WMA in 17%^{60,64} and 38%.⁶⁶ WMA are variably reported as present more often in adult migraineurs more than 40 years old and less than 60^{64,71} and equally present⁶⁶ compared with those 40 or younger. Cooney and coworkers⁶⁴ found an increased frequency of WMA associated with age over 50 and with medical risk factors (hypertension, atherosclerotic heart disease, diabetic mellitus, autoimmune disorder, or demyelinating disease) but not with gender, migraine subtype, or duration of migraine symptoms.

Migraine with aura is associated with an increased frequency of right-to-left shunts, mostly resulting from patent foramen ovale, which hypothetically could cause WMA as a result of paradoxical microembolism of platelets or the shunting of vasoactive amines, which have escaped the pulmonary circulation. A study of 185 consecutive subjects who had migraine with aura, 66% with right-to-left shunts, however, found no increase in white matter lesion load as compared with those who did not have shunts.⁷² Periventricular WMA were present in 19% and deep WMA in 46%, and 11% showed coexistence of periventricular and deep lesions. Similarly, there was no increase in white matter lesions in another consecutive series of 87 migraineurs, 45% of whom had right-to-left shunts.⁷³ WMA were present in 61% of patients. In both studies, the only risk factor associated with WMA was older age but not gender, frequency of migraines, smoking, hyperlipidemia, or oral contraceptive use.

In a series of 16 consecutive migraineurs (14 who did not have aura and 2 who had aura), Rovaris and colleagues⁷⁰ found white matter lesions in five (31%). The pattern of MRI lesions fulfilled diagnostic criteria suggestive of MS in four—none of the patients had any other neurologic symptoms or signs. Cervical spine MRI studies were

obtained in all subjects and in 17 age- and gender-matched controls with the detection of no cord lesions.

Kruit and coworkers⁷⁴ obtained MRI scans in a population-based sample of Dutch adults, ages 30 to 60, who had migraine with aura ($n = 161$) or migraine without aura ($n = 134$) and in well-matched controls ($n = 140$). No participants reported a history of stroke or transient ischemic attack or had relevant abnormalities at standard neurologic examination. There was no significant difference between patients who had migraine and controls in overall infarct prevalence (8.1% versus 5%). In the cerebellar region of the posterior circulation territory, however, patients who had migraine had a higher prevalence of infarct than controls (5.4% versus 0.7%). The adjusted odds ratio (OR) for posterior infarct varied by migraine subtype and attack frequency. The adjusted OR was 13.7 for patients who had migraine with aura compared with controls. In patients who had migraine with a frequency of attacks of one or more per month, the adjusted OR was 9.3. The highest risk was in patients who had migraine with aura with one attack or more per month (OR 15.8). Kruit and colleagues⁷⁵ hypothesize that focal (possibly migraine-related) hypoperfusion rather than microembolic occlusion is responsible for most of the cerebellar infarcts.

Thirty eight percent of the subjects in the migraine and control groups had at least one medium-sized deep white matter lesion (DWML). Among women, the risk for high DWML load was increased in patients who had migraine compared with controls (OR 2.1); this risk increased with attack frequency (highest in those who had one attack per month; OR 2.6) but was similar in patients who had migraine with or without aura. In men, control patients and patients who had migraine did not differ in the prevalence of DWMLs. There was no association between severity of periventricular white matter lesions (PVWMLs) and migraine, irrespective of gender or migraine frequency or subtype. There were no differences in the distributions and the mean values of grades of severity of PVWMLs between patients who had migraine and controls. These results did not vary by gender, migraine subtype, or migraine attack frequency.

Kruit and colleagues⁷⁶ further reported the brainstem and cerebellar hyperintense lesions found in their same migraine population. Infratentorial hyperintensities were identified in 13 of 295 (4.4%) migraineurs and in 1 of 140 (0.7%) controls. Twelve patients had hyperintensities, mostly bilateral, in the dorsal basis pontis (described for the first time in migraine). Those who had infratentorial hyperintensities also had supratentorial white matter lesions more often. The cause may be small-vessel disease (arteriosclerosis), repetitive perfusion deficits, or both.

Although the cause of WMA in migraine is not certain, various hypotheses have been advanced, including increased platelet aggregability with microemboli, abnormal cerebrovascular regulation, and repeated attacks of hypoperfusion during the aura.^{59,65,67,74} The presence of antiphospholipid antibodies might be another risk factor for WMA in migraine.⁷⁷ The reported incidence of antiphospholipid antibodies in migraine ranges from 0%⁷⁸ to 24%.⁶⁸ In one MRI study, however, the presence of WMA showed no correlation with the presence of anticardiolipin antibodies.⁵⁹ The presence of anticardiolipin antibodies is not an additional risk factor for stroke in migraineurs.⁷⁹ Tietjen and colleagues⁸⁰ found that, compared with control subjects, there was no increase in frequency of anticardiolipin positivity in adults under age 60 who had transient focal neurologic events or in those who had migraine with or without aura.

A subgroup of migraineurs may have a genetic predisposition for white matter lesions on MRI scans. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a familial genetic disease with migraine as a common symptom and severe WMA on MRI as a consistent

neuroimaging finding. Chabriat and colleagues⁸¹ described several members of a family who had an autosomal dominant illness manifested by migraine attacks and a significant leukoencephalopathy on MRI but without other specific manifestations of CADASIL. Mourad and colleagues⁸² also describe four patients over age 60 who had typical Notch3 mutations leading to CADASIL and who did not have dementia or disability but had extensive WMA on MRI. It is possible that there is a specific gene locus for migraine with white matter changes. Variable gene penetrance could result in CADASIL at one extreme and individuals who have tiny T2 hyperintense white matter foci and migraine alone at the other extreme.

Cerebral Atrophy

Diffuse cerebral atrophy with widening of the lateral ventricles and cerebral sulci is detected equally well by MRI and CT scans.⁶³ The incidence of cerebral atrophy in migraineurs on CT and MRI scans has been variably reported as 4%,⁵⁵ 26%,⁵⁷ 28%,⁷¹ 35%,⁶³ and 58%.⁸³ Studies describe most cases of atrophy as mild to moderate. The cause of the atrophy, which can be a nonspecific finding based on often subjective criteria, is not certain.^{69,71,84} Three more recent studies have found the incidence of atrophy in migraineurs no greater than in controls.^{65,69,84} The high incidence of CT changes seen in migraineurs in early studies probably reflects artifact and a failure to recognize the range of normality of this new imaging technique.

Arteriovenous Malformations, Brainstem Vascular Malformations, and Migraine

The prevalence of AVMs is approximately 0.5% in postmortem studies.⁸⁵ In contrast to saccular aneurysms, up to 50% of patients present with symptoms or signs other than hemorrhage. Headache without distinctive features (such as frequency, duration, or severity) is the presenting symptom in up to 48% of cases.⁸⁶

Migraine-like headaches with and without visual symptoms can be associated with AVMs especially those in the occipital lobe, the predominant location of approximately 20% of parenchymal AVMs.^{87,88} Although headaches always occurring on the same side (side-locked) are present in 95% of patients who have AVMs,⁸⁹ 17% of those who have migraine without aura and 15% of patients who have migraine with aura have side-locked headaches.⁹⁰

Migraine resulting from an AVM usually is atypical and rarely meets International Headache Society (IHS) criteria for migraine. In a series of 109 patients who had headache and AVMs, Ghossoub and colleagues⁹¹ reported the following features: nonpulsating, 95%; nausea, vomiting, light, or noise sensitivity, 4.1%; unilateral and homolateral to the AVM, 70%; duration less than 3 hours, 77%; 1 to 2 per month, 82.5%; and usually mild, responding to simple analgesics. Bruyn⁸⁹ reported the following features in patients who had migraine-like symptoms and AVM: unusual associated signs (papilledema, field cut, and bruit), 65%; short duration of headache attacks, 20%; brief scintillating scotoma, 10%; absent family history, 15%; atypical sequence of aura, headache, and vomiting, 10%; and seizures, 25%.

The following brainstem vascular malformations are associated with migraine meeting IHS criteria: a hemorrhagic midbrain cavernoma resulting in a contralateral headache,⁹² a pontine bleed from a cavernous angioma with initially ipsilateral headache then bilateral with aura,⁹³ pontine capillary telangiectasia with signs of residual hemorrhage with bilateral headaches initially with aura,⁹⁴ and a midbrain/upper pons hemorrhagic AVM/cavernous malformation resulting in a contralateral headache with aura.⁹⁵ These malformations provide evidence for the involvement of the brainstem in the initiation of migraine.

Chronic Migraine

American Academy of Neurology practice parameter

A report of the Quality Standards Subcommittee of the AAN⁵⁴ makes the following recommendation: “Neuroimaging is not usually warranted in patients with migraine and a normal neurologic examination (Grade B).”

Although the yield is low, **Box 4** lists some reasons to consider neuroimaging in migraineurs.

Trigeminal autonomic cephalalgias

TACs are primary headache syndromes characterized by severe short-lasting headaches typically associated with paroxysmal facial autonomic symptoms. TACs include cluster headache, paroxysmal hemicrania, and short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT), with cluster headache the most common.^{96,97}

There are 35 case reports of patients who had TACs and TAC-like syndromes (including 20 diagnosed as cluster headaches) showing significant improvement or even disappearance of the headache after therapeutic intervention aimed at the structural lesion (eg, surgery, embolization, radiotherapy, or medical therapy).^{98–101} Only 10 of the patients had atypical symptoms, including abnormal attack duration, absence of autonomic symptoms, bilateral autonomic symptoms, or a continuous headache. Patients could have a large cerebral tumor and still meet IHS criteria for a TAC. Secondary causes were as follows: vascular abnormalities, including AVMs, fistula, aneurysms, and arterial dissections (11 patients); tumors (19 patients, including 12 who had pituitary tumor); abnormalities in paranasal sinuses (aspergilloma, foreign object, and mucocoele) (three patients); and cervical syrinx (one patient).

Levy and colleagues¹⁰² reported a series of 84 consecutive patients who had pituitary tumors (65% macroadenomas). Using IHS classification, four met criteria for SUNCT, three for cluster, and one for HC. Cavernous sinus invasion was present in two of the three cluster cases. Of the four SUNCT cases, two were prolactinomas

Box 4

Reasons to consider neuroimaging in migraineurs

- Unusual, prolonged, or persistent aura
- Increasing frequency, severity, or change in clinical features
- First or worst migraine
- Basilar
- Confusional
- Hemiplegic
- Late-life migraine accompaniments
- Aura without headache
- Headaches always on the same side?
- Posttraumatic
- Patient or family and friend request

From Evans RW. Diagnosis of headaches and medico-legal aspects. In: Evans RW, Mathew NT, editors. Handbook of headache. 2nd edition. Philadelphia: Lippincott-Williams & Wilkins; 2005. p. 21; with permission.

and two were growth hormone–secreting tumors. Although information is provided on response of all headaches to treatment, response to treatment of the TACs is not provided.

Hemicrania continua According to the IHS second edition,¹⁰³ to meet the criteria for HC, another TAC, the headache should be present for more than 3 months with all of the following characteristics: unilateral without side-shift; daily and continuous, without pain-free periods; moderate intensity, but with exacerbations of severe pain; and with a complete response to indomethacin. During exacerbations, the headache must have one of the following ipsilateral features: conjunctival injection or lacrimation; nasal congestion or rhinorrhea; and ptosis or miosis. The headaches usually are unremitting but rare cases of remission are reported. HC can be easily confused with chronic migraine, as approximately 75% who have HC have exacerbations of severe throbbing or stabbing pain, which can be associated with photophobia (59%), phonophobia (59%), nausea (53%), and vomiting (24%).¹⁰⁴ The exacerbations can last from 20 minutes to several days with pain awakening one third of patients. Autonomic features are present in up to 75% with tearing and then conjunctival injection the most common. Thus, a trial of medication effective for HC, such as indomethacin, should be considered for any patient who has chronic unilateral headache that might be HC but can be easily misdiagnosed as migraine.

Rarely, HC many have a secondary cause, which includes the following:¹⁰⁵ mesenchymal tumor of the sphenoid, lung malignancy, HIV (causal association unclear), C7 root irritation reported to aggravate, left lateral medullary infarction with left vertebral artery occlusion on MRI and MR angiography (head pain contralateral to infarction), internal carotid artery dissection, unruptured cavernous internal carotid artery aneurysm,¹⁰⁶ prolactinoma (headache exacerbation with dopamine agonists), venous malformation of the right masseter; sphenoid sinusitis,¹⁰⁷ and cerebellopontine angle epidermoid.¹⁰⁸ Although the yield is probably low, MRI scan of the brain is reasonable when initially evaluating patients presenting with symptoms consistent with HC.

Patients meeting IHS criteria for a TAC rarely have a secondary cause for their headache detected on neuroimaging. Appropriate testing is indicated, however, if atypical symptoms and signs are present.

New daily persistent headache **Box 5** lists some primary and secondary causes of NDPHs present for more than 3 months. NDPH is a diagnosis of exclusion. Some of these secondary disorders may have a thunderclap or sudden onset of severe headache whereas others may develop gradually over 1 to 3 days and meet the onset period criteria for NDPH. New-onset daily headaches with a normal neurologic examination also could be the result of various other causes, particularly when seen within the first 2 months after onset, including postmeningitis headache, chronic meningitis, brain tumors, leptomeningeal metastasis, temporal arteritis, chronic subdural hematomas, posttraumatic headaches, sphenoid sinusitis, and hypertension. When the headaches have been present for more than 3 months with a normal neurologic examination, the yield of testing is low. A few additional examples are discussed.

Spontaneous intracranial hypotension (SIH) syndrome often presents as a headache that is present when patients are upright but is relieved by lying down or as an orthostatic headache. As SIH syndrome persists, however, a chronic daily headache may be present without orthostatic features. SIH syndrome also may present as other types of headache, including exertional without any orthostatic features, acute thunderclap onset, paradoxical orthostatic headache (present in recumbency and relieved

Box 5**Differential diagnosis of new daily headaches present for more than 3 months***Primary headaches*

NDPH

Chronic migraine

Chronic tension-type

Combined features

HC

Secondary headaches (NDPH mimics)

Postmeningitis headache

Chronic meningitis

Primary with medication rebound

Neoplasms

Chronic subdural hematoma

Posttraumatic headaches

Sphenoid sinusitis

Hypertension

Low CSF pressure syndrome

Cervical artery dissections

Pseudotumor cerebri (idiopathic and secondary intracranial hypertension)

CVT

AVM

Chiari malformation

Temporal arteritis

Cervicogenic

Temporomandibular joint dysfunction

when upright), and intermittent headache resulting from intermittent leaks, or as the acephalgic form with no headache at all.¹⁰⁹ Neck or interscapular pain may precede the onset of headache in some cases by days or weeks. MRI abnormalities of the brain and spine are variably present in approximately 90% of cases. An MRI scan of the brain may reveal diffuse pachymeningeal (dural) enhancement with gadolinium without leptomeningeal (arachnoid and pial) involvement and, in some cases, subdural fluid collections, which return to normal with resolution of the headache.^{109,110}

Cervical artery dissections, which can present with headache or neck pain alone,¹¹¹ can be a rare cause of new daily headaches.¹¹² Occasionally, the headaches can persist intermittently for months and even years and can lead to a pattern of chronic daily headaches especially after cervical carotid artery dissection.

Headache is present in up to 90% of cases of CVT and often is the initial symptom and occasionally the only symptom.¹¹³ The headache can be unilateral or bilateral in any location, mild to severe, and intermittent or constant. The onset usually is subacute but can be sudden or thunderclap. The headache almost always is associated with other neurologic signs, such as papilledema, focal deficits, seizures,

disorders of consciousness, or cranial nerve palsies. CVT can be a mimic of idiopathic intracranial hypertension.

Neuroimaging studies have variable sensitivities in diagnosing CVT. CT will diagnose only approximately 20% of cases of CVT when demonstrating the hyperdensity of the thrombosed sinus on plain images and the delta sign seen with superior sagittal sinus thrombosis after contrast administration. Helical CT venography is a sensitive diagnostic method. CVT may be missed on routine MRI imaging of the brain although echo-planar T2*-weighted MRI may increase the sensitivity.¹¹⁴ MRV increases the sensitivity of MR especially within the first 5 days of onset or after 6 weeks. CVT also can be demonstrated on digital subtraction venography.

Chiari I malformation typically is a congenital malformation of cerebellar tonsillar herniation at least 5 cm below the foramen magnum. The headache attributed to Chiari I malformation is occipital or nuchal-occipital with occasional radiation unilaterally to frontotemporal or shoulder regions and sometimes generalized.³⁸ The pain may be dull, aching, or throbbing and may last less than 5 minutes to several hours to days. Pain may be precipitated by neck flexion or palpation or coughing.

In an imaging study of children, ages 2 to 18, who had headaches,¹¹⁵ Chiari type I malformation was identified in 14 of 241 (5.8%) patients. Five of 14 (35.7%) patients who had Chiari I malformation had headaches secondary to their malformation. Three patients had surgical decompression with significant headache relief in two. The other nine patients were diagnosed with migraine (35.7%) and tension-type (28.6%) headaches. In adults, one study found an association of chronic migraine with Chiari I.¹¹⁶ Although headache is the most common presenting complaint of Chiari I malformation, the malformation typically is an incidental finding on MRI studies done for primary headaches.

Secondary pathology should be considered especially when NDPH occurs over age 50. In a study of those over age 65 age who had new-onset headaches, the prevalence of secondary headaches resulting from serious pathology was 15%.¹¹⁷ Temporal arteritis always should be considered but the diagnosis often is delayed, especially in those under age 70.¹¹⁸ Temporal arteritis rarely occurs under age 50, with most biopsy-proved large series having no patients under age of 50.¹¹⁹ A Canadian study reveals the rare exception: of 141 consecutive patients presenting to a neuro-ophthalmology practice, there was one patient under age 50 (age 47).¹²⁰

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